18. (Amended) The method of Claim 17, wherein said chimeric antibody is administered for four weeks.

19. (Amended) The method of Claim16, wherein said chimeric anti-CD20 antibody is produced by a transfectoma which has been deposited in TCAE8, ATCC deposit number 69119.

Please enter new claims 21 and 22 as follows.

--21. A method of treating a human patient suffering from B-cell lymphoma comprising the following steps:

(i) administration of a non-radiolabeled chimeric anti-CD20 antibody which itself when administered at a dosage of about 0.4 mg/kg body weight results in nearly complete peripheral B-cell depletion within about 24 hours post treatment infusion; and

(ii) administration of at least one chemotherapeutic agent;

wherein said chimeric anti-CD20 antibody is produced by a transfectoma which has been deposited in TCAE8, ATCC deposit number 69119.

22. The method of claim 21, wherein the at least one chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone.--

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.116, and in light of the remarks which follow are respectfully requested.

The indication in paragraph 10 of the Official Action that claims 14 and 15 would be allowable if rewritten in independent form is noted with appreciation. Applicants have replaced claims 14 and 15 with independent claim 21 and claim 22, depending therefrom. Thus, the objection should be withdrawn and, at the very least, claims 21 and 22 are expected to be allowed in the next Official Action.

By the present amendment, claim 11 have been amended to recite that the anti-CD20 antibody possesses the recited B cell depleting activity at 0.4 mg/kg. This amendment cannot raise new issues as this dosage was explicitly part of the prior claim as well as claim 16 which recites that the administered chimeric anti-CD20 antibody possess the recited B cell depleting

activity at any dosage between about 0.4 to about 20.0 mg/kg body weight. Also, in order to expedite prosecution, "about" has been deleted from claims 11 and 16. However, it should be noted that Applicants continue to disagree with the Examiner's extremely liberal interpretation of "about" in relation to the prior art.

Turning now to the outstanding rejections, the objection in the oath is noted. A substitute oath will be provided on allowance.

Claims 18-20 stand rejected based on §112 second paragraph. This rejection is moot in view of the amendment of claim 18 herein.

Claims 11-13 and 16-18 continue to be rejected based on Press et al. (Blood) in view of Hellstrom et al. (WO 92/07466) and Robinson et al. (U.S. Patent 5,550,362). This rejection is respectfully traversed.

At the outset it should be emphasized that all the present claims require administration of a chimeric antibody specific to CD20 which when administered at a dosage of 0.4 mg/kg results in substantially total B cell depletion after 24 hours.

The administration of an antibody having such depleting function is not fairly suggested by the prior art references if such references are accorded their reasonable meaning as they would be construed by one skilled in the art.

The first reference, Press et al. (Blood) certainly does not teach a method. As previously argued, the reference only described a murine anti-CD20 antibody having substantially less depleting activity, which needs to be administered at substantially higher dosages, in excess of 0.4 mg/kg to achieve substantial B cell depletion.

Also, applicants respectfully maintain that Press et al. actually teaches away from the claimed invention.

In particular, Press et al. is quite clear that substantially higher does (higher than 0.4 mg/kg) need to be administered to achieve relatively transient depletion results. Indeed, it appears that 10 mg/kg (dose in Table 2 that the Examiner seemingly refers to) is at the low end of the dose range disclosed by Press et al. and that Press et al. actually recommend that for effective therapy doses of 1 and > 2g are optimal for achieving desired results (optimal B cell depletion). Therefore, one skilled in the art reading this reference would not reasonably conclude that it suggests administration of a chimeric anti-CD20 antibody having the recited B cell depleting activity at a dosage of 0.4 mg/kg. Thus, Press et al., especially given the

present amendments does not suggest the claimed invention and in fact actually teaches away from the claimed therapeutic method.

Particularly, the relatively high dosage ranges that are disclosed by Press et al. to be required can not render obvious the unexpectedly low dose of antibody (0.4 mg/kg) that achieves substantially total B cell depletion for an antibody according to the claimed methods. The addition of Hellstrom et al. and Robinson et al. does not overcome the deficiencies of the rejection. While it is certainly agreed that chimeric antibodies containing human constant regions typically possess greater effector function than human murine antibodies this is insufficient to render the claimed therapeutic methods obvious given the required degree of the B cell depleting activity of an antibody according to the present invention. Particularly, it could not be reasonably predicted from either Hellstrom et al. or Robinson et al. that a chimeric anti-CD20 antibody, as claimed, would result in substantially total B cell depletion when administered at a relatively low dosage, namely 0.4 mg/kg, after only 24 hours.

In particular, there is no teaching in any of prior art references cited by the Examiner, or known to Applicants which would suggest a method of treating B cell lymphoma using a chimeric antibody possessing these significant B cell depleting properties.

The Examiner has alleged that Press et al. suggest a dosage of 10mg/m^2 to achieve a B cell depletion which is encompassed by the claimed invention. However, it is respectfully submitted that the Examiner is misconstruing the reference. If fairly construed, Press et al. teaches that their IF5 antibody, if used to achieve optimal (maximal B cell depletion), should be administered at a total dose of 1 to 2 grams. If the Examiner's calculation if what the reference suggests were correct to achieve the claimed outcome (supposedly .27 mg/kg) this would translate to a total antibody dosage (based on an average 75kg human subject cited are by the Examiner) of only 172.5 milligrams (75kg) (.27 mg/kg)=172.5mg, milligrams).

Also, it should be noted that Press et al. achieve this level of B cell depletion in combination with a chemotherapeutic agent. By contrast, the subject claims provide that the administered antibody itself is able to achieve substantially total B cell depletion at a dosage of only 0.4 mg/kg after only 24 hours. This is not inherent to the Press et al. reference, irrespective of the Examiner's continued suggestion to the contrary. Indeed, such a suggestion is unreasonable, since it is contrary to the express teachings of the reference as to the high required dosages and transient nature of the observed B cell depletion responses. If

such results were truly achieved at the dosages alleged by the Examiner, Press et al. would not recommend the disclosed higher dosages (1-2g) especially given the known adverse effects (HAMA responses) of murine antibodies. Quite clearly, it would not make good sense.

Therefore, based on the foregoing, withdrawal of the §102 rejection based on Press et al. in view of Hellstrom and Robinson et al. is respectfully requested.

It is hoped and anticipated that this response should place this case in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

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Attachment:
Appendix

APPENDIX

11. (Amended) A method of treating a human patient suffering from B-cell lymphoma comprising the following steps:

(i) administration of a non-radiolabeled chimeric anti-CD20 antibody which itself when administered at a dosage of ~~about~~ 0.4 mg/kg body weight results in nearly complete peripheral B-cell depletion within about 24 hours post treatment infusion; and

(ii) administration of at least one chemotherapeutic agent.

16. (Amended) A method of treating a human patient suffering from B cell lymphoma comprising the following steps:

(i) administration of a non-radiolabeled chimeric anti-CD20 antibody which itself when administered at any dosage between ~~about~~ 0.4 to ~~about~~ 20.0 mg/kg body weight results in nearly complete peripheral B cell depletion within about 24 hours post treatment infusion; and

(ii) administration of at least one chemotherapeutic agent.

18. (Amended) The method of Claim 17, wherein said chimeric antibody is administered ~~four~~ for four weeks.

19. (Amended) The method of Claim ~~11~~16, wherein said chimeric anti-CD20 antibody is produced by a transfectoma which has been deposited in TCAE8, ATCC deposit number 69119.

--21. A method of treating a human patient suffering from B-cell lymphoma comprising the following steps:

(iii) administration of a non-radiolabeled chimeric anti-CD20 antibody which itself when administered at a dosage of about 0.4 mg/kg body weight results in nearly complete peripheral B-cell depletion within about 24 hours post treatment infusion; and

(ii) administration of at least one chemotherapeutic agent;

wherein said chimeric anti-CD20 antibody is produced by a transfectoma which has been deposited in TCAE8, ATCC deposit number 69119.

22. The method of claim 21, wherein the at least one chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone.--